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ORIGINAL ARTICLE

Substrate metabolism during exercise in the spinal cord injured

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Abstract The primary aim of the study was to examine substrate metabolism during combined passive and active exercise in individuals with spinal cord injury (SCI). Nine men and women with SCI (mean age 40.6 ± 3.4 years) completed two trials of submaximal exercise 1 week apart. Two maintained a complete injury and seven had an incomplete injury. Level of injury ranged from thoracic (T4–T6 and T10) to cervical (four C5–C6 and three C6–C7 injuries). During two bouts separated by 1 week, subjects completed two 30 min sessions of active lower-body and passive upper-body exercise, during which heart rate (HR) and gas exchange data were continuously assessed. One-way analysis of variance with repeated measures was used to examine differences in all variables over time. Results demonstrated significant increases ($P < 0.05$) in HR and oxygen uptake (VO_2) from rest to exercise. Respiratory exchange ratio (RER) significantly increased ($P < 0.05$) during exercise from 0.85 ± 0.02 at rest to 0.95 ± 0.01 at the highest cadence, reflecting increasing reliance on carbohydrate from 50.0 to 83.0% of energy metabolism. Data demonstrate a large reliance on carbohydrate utilization during 30 min of exercise in persons with SCI, with reduced contribution of lipid as exercise intensity was increased. Strategies to reduce carbohydrate utilization and increase lipid oxidation in this population should be addressed.

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Introduction

Substrate metabolism during exercise is determined primarily by exercise intensity and duration. It is well-established that with increasing exercise intensity, there is decreased reliance on lipid and enhanced reliance on carbohydrate to meet the high rates of adenosine triphosphate (ATP) demand (Romijn et al. 1993). In endurance-trained populations, there is a relative sparing of muscle glycogen and increased use of lipid primarily from intramuscular stores that contribute to enhanced exercise performance (Hurley et al. 1986). Greater mitochondrial density and respiratory capacity and enhanced activity of mitochondrial enzymes (Holloszy and Coyle 1984) explain this alteration in substrate metabolism with training.

In persons with spinal cord injury (SCI), there is impaired neural function below the level of injury (Kjaer et al. 1987), altering heart rate (HR), blood pressure, and catecholamine release (Dela et al. 2003). Karlsson et al. (1997) reported significantly lower levels of epinephrine and norepinephrine both at rest and during mental and physical stress in persons with SCI with injury above T5 compared to able-bodied subjects. Yet at rest, lipolysis was preserved in persons with SCI. Catecholamine release stimulates degradation of muscle glycogen and adipose free fatty acid (FFA) during exercise (Karlsson et al. 1997), so removal of sympathetic input may diminish this response.

A few studies have documented alterations in substrate use during exercise in the SCI. During electrically-stimulated leg cycling at a workload equal to 75% maximal oxygen uptake (VO_{2max}), respiratory exchange ratio (RER),

Table 1 Demographic characteristics of subjects ($N = 9$)

Gender	Age (year)	Mass (kg)	Height (m)	Injury duration (year)	Training duration (year)	Injury level	Injury status	ASIA score
Male[a]	49	77.0	1.7	4.0	3.5	C5–C6	Incomplete	B
Male	37	84.0	1.6	1.5	0.5	C5	Incomplete	B
Female	26	63.5	1.6	6.0	6.0	C6–C7	Incomplete	C
Male	26	79.5	1.8	6.0	6.0	C6	Incomplete	C
Female	47	52.5	1.6	20.0	0.0	C5–C6	Incomplete	X
Male	35	75.0	1.7	1.3	1.0	T4–T6	Incomplete	X
Male	54	81.8	1.8	3.0	3.0	T10	Complete	X
Male	48	75.0	1.8	3.5	0.5	C7	Incomplete	X
Male	43	81.8	1.8	3.5	2.5	C5–C6	Complete	X
Mean ± SE	40.6 ± 3.4	74.5 ± 3.4	1.7 ± 0.3	5.4 ± 1.9	2.6 ± 0.8			

SE standard error, *X* unavailable

[a] This subject was unable to complete the second exercise trial

glucose uptake, and phosphocreatine degradation were significantly higher ($P < 0.05$) in SCI subjects versus able-bodied controls exercising on a cycle ergometer (Kjaer et al. 2001), yet plasma glycerol and FFA delivery to the leg were lower. In wheelchair athletes ($VO_{2max} = 35.9$ mL/kg per min), 20 min of arm cranking at 55–75% VO_{2max} revealed a maintenance of fat oxidation and a marked increase in carbohydrate oxidation to 1.7 g/min at the highest intensity (Knechtle et al. 2003). During simulated wheelchair racing at 55, 65, and 75% VO_{2max} performed on a treadmill, fat oxidation did not change, yet carbohydrate oxidation and lactate concentration significantly increased, reflecting increased anaerobic metabolism (Knechtle et al. 2004). Investigation of this topic in the SCI is important, as their life expectancy is approaching that of the able-bodied (Fawcett et al. 2007), and many thousands partake in athletic endeavors such as tennis, basketball, and endurance racing that are dependent upon adequate delivery of substrate.

The primary aim of the study was to investigate alterations in substrate metabolism during exercise in relatively untrained men and women with SCI, as the preponderance of data in this population is derived from athletes. It is hypothesized that carbohydrate will be the primary substrate utilized during exercise.

Methods

Participants

Nine men and women with SCI initiated the study; their characteristics are demonstrated in Table 1. ASIA scores were only available for four subjects. One subject was sedentary, three completed between 1 and 3 h of exercise per week, and five participated in 6–8 h of weekly physical activity. Injury level ranged from thoracic (T4–T6 and T10) to cervical (four C5–C6 and three C6–C7 injuries). There were two paraplegics and seven tetraplegics, respectively. Subjects were recruited by word-of-mouth and flyers distributed at rehabilitation centers in southern California. Participants were free of known cardiac, pulmonary, or metabolic disease, and were not on medications that affect cardiovascular or metabolic function. Subjects filled out a health-history questionnaire and provided informed consent before participating in the study. All experimental procedures were approved by the University Institutional Review Board and comply with the Declaration of Helsinki.

Exercise protocol

After refraining from caffeine, alcohol, and exercise for 24 h, and completing a 4 h fast, subjects arrived at the laboratory for the first trial. They completed 24 h dietary recalls and standardized their food intake in the day before each trial. Subjects remained in their wheelchair, and their chair was secured inside the rails of the exercise device (Flexiciser™ Sport, Carlsbad, CA, USA). Their feet were attached to the machine's pedals with Velcro straps, and they grabbed the handgrips with the use of Velcro straps supplied by the manufacturer. They initially completed 3–5 min of passive warm-up at 30 rev/min, during which the machine, via a motor, executed movement of the arms and legs. This was performed to reduce spasticity and familiarize the subject with the exercise mode (Figoni et al. 1990). In all subjects, this tended to increase oxygen uptake (VO_2) and carbon dioxide production (VCO_2) by approximately two fold compared to baseline. This was followed by 30 min of exercise, in which subjects were asked to actively resist the pedals with their legs to the best of their ability, yet passively use their arms and upper-body, as recently described (Astorino et al. 2008; Muraki et al. 1996). In seven of nine subjects, this continued to increase

VO_2 compared to the warm-up. If unable to resist the pedals, subjects were asked to visualize using the legs to resist movement of the pedals. Active upper-body exercise was not required, as only two subjects (the paraplegics) had full use of their upper-body or sufficient use of their hands to resist the machine, which would contribute to higher energy expenditure. Cadence of the machine was set at 15 rev/min for the first 10 min and increased to 30 and 45 rev/min at minute 10 and 20. In 15 subjects with chronic injury at T3–T12, passive leg exercise at a similar cadence (40 rev/min) enhanced blood flow velocity in the femoral artery compared to rest (Ballaz et al. 2007). This protocol was repeated 1 week later at the same time of day. Subjects adhered to similar pre-test guidelines mandated in the 24 h before the second trial.

Assessment of gas exchange data

Throughout exercise, gas exchange data were obtained using indirect calorimetry (ParvoMedics True One 2400, Sandy, UT). Expired volume was measured using a Hans Rudolph pneumotach flowmeter, then integrated. VO_2 and VCO_2 were measured using the Servomex paramagnetic O_2 analyzer and infra-red CO_2 analyzer, respectively. Before exercise, the metabolic cart was calibrated to gases of known concentration (16.01% O_2 and 4.00% CO_2) as well as to room air (20.93% O_2 and 0.03% CO_2), and a 3 l syringe was used to calibrate flow. Pilot testing revealed a test/retest correlation of VO_2 across multiple days equal to 0.94. HR was assessed during exercise via telemetry (Polar Electro, Woodbury, NY, USA).

Assessment of substrate metabolism

Oxygen uptake (VO_2) and carbon dioxide production (VCO_2) values were obtained every 15 s. Data were averaged every 5 min and were used to calculate RER. Percent contribution of fat and carbohydrate was calculated using the following equation:

$$\%\text{fat} = [1 - \text{RER}/0.3] \times 100.$$

Rates of carbohydrate and fat oxidation were calculated using established equations (Frayn 1983), with the contribution of protein assumed to be negligible.

$$\text{Rate of fat oxidation (g/min)} = 1.67(VO_2) - 1.67(VCO_2)$$

$$\text{Rate of CHO oxidation (g/min)} = 4.55(VCO_2) - 3.21(VO_2)$$

These values were then multiplied by coefficients for fat (9 kcal/g) and carbohydrate (4 kcal/g) to yield rates of fat and carbohydrate oxidation in kcal/min.

Data analysis

Data were expressed as mean ± standard error (SE) and analyzed using SPSS Version 14.0 (Chicago, IL, USA). One-way analysis of variance (ANOVA) with repeated measures was used to examine gas exchange data (VO_2, VCO_2, ventilation (V_E), and RER) and substrate responses across time during exercise. If a significant F ratio was obtained, Tukey's post hoc test was used to locate differences between means. Because variables examined across days of testing were consistent ($P > 0.05$), all data reported are the average of two trials. Statistical significance was set at $P < 0.05$.

Results

Testing was well-tolerated by all subjects without reports of pain or discomfort. Because of personal issues, one subject, a male quadriplegic with injury at C5–C6, did not complete his second trial.

Gas exchange and heart rate data

Exercise significantly ($P < 0.01$) increased VO_2 compared to rest (0.21 ± 0.03 L/min, 95% confidence interval (CI) = 0.14–0.29 L/min). VO_2 significantly increased ($P < 0.05$) during exercise compared to the previous cadence. These data are demonstrated in Table 2.

There was a significant increase in VCO_2 with exercise ($P < 0.01$). A twofold increase ($P < 0.05$) in VCO_2 was observed from rest (0.17 ± 0.03 L/min, 95% CI = 0.10–0.24 L/min) to warm-up (0.33 ± 0.03 L/min, 95% CI = 0.27–0.39 L/min), with sustained increases in VCO_2 demonstrated as cadence was increased (Table 2). However, at a cadence of 45 rev/min, VCO_2 did not significantly increase compared to 30 rev/min.

Respiratory exchange ratio significantly increased ($P < 0.05$) from 0.85 ± 0.07 (95% CI = 0.80–0.91) at rest to 0.91 ± 0.06 (95% CI = 0.87–0.96) during warm-up to 0.95 ± 0.04 (95% CI = 0.92–0.98) at 45 rev/min (Table 2). However, only exercise at 30 and 45 rev/min demonstrated significant ($P < 0.05$) increases in RER compared to the warm-up or exercise at 15 rev/min (Table 2).

Ventilation was significantly augmented with exercise ($P < 0.01$). At all time points, V_E was significantly different ($P < 0.05$) from each other with the exception of V_E at 10 and 15, 15 and 20, and 25 and 30 min (Table 2).

The HR response to combined passive and active exercise is revealed in Table 2. Heart rate was significantly augmented from rest (63.5 ± 3.4 b/min, 95% CI = 55.4–71.6 b/min) to exercise at all cadences ($P < 0.01$).

Table 2 Gas exchange and heart rate responses to combined passive and active exercise in persons with SCI

Time (min)	Cadence (rev/min)	VO_2 (L/min)	VCO_2 (L/min)	V_E (L/min)	RER	HR (b/min)
Rest	NA	0.21 ± 0.03	0.17 ± 0.03	9.56 ± 0.77	0.85 ± 0.02	63.5 ± 3.4
Warm-up	30	0.36 ± 0.03*	0.33 ± 0.03*	12.53 ± 0.93*	0.91 ± 0.02*	70.9 ± 3.4*
5	15	0.43 ± 0.18*,**	0.39 ± 0.02*,**	15.05 ± 0.76*	0.91 ± 0.03*	79.5 ± 1.8*
10	15	0.44 ± 0.04*,**	0.41 ± 0.03*,**	15.12 ± 0.87*	0.92 ± 0.02*	84.6 ± 1.2*
15	30	0.51 ± 0.04*,**	0.47 ± 0.04*,**	19.27 ± 1.17*	0.95 ± 0.02*	85.8 ± 2.2*
20	30	0.51 ± 0.04*	0.48 ± 0.04*	19.25 ± 1.41*	0.95 ± 0.03*	82.3 ± 1.5*
25	45	0.59 ± 0.06*,**	0.54 ± 0.05*	21.69 ± 1.31*	0.93 ± 0.02*	87.3 ± 1.6*
30	45	0.56 ± 0.06*,**	0.54 ± 0.05*	21.79 ± 1.51*	0.95 ± 0.01*	88.1 ± 2.3*

Data are reported as mean ± SE

* $P < 0.05$ from rest; ** $P < 0.05$ from previous exercise cadence

However, it was significantly increased ($P < 0.05$) from the warm-up only at 30 and 45 rev/min.

Percent carbohydrate and fat oxidation

With increasing cadence, there was a gradual, sustained increase in carbohydrate oxidation ($P < 0.05$) and decrease ($P < 0.05$) in fat oxidation (Fig. 1). Fat provided 50 ± 3.1% of ATP at rest, yet during exercise, fat use declined and ranged from 17 to 30%. In contrast, dependence upon carbohydrate was higher and ranged from 70 to 83%.

Rates of carbohydrate and fat oxidation

Rates of carbohydrate and fat oxidation are demonstrated in Fig. 2. With increasing exercise intensity, there was augmented carbohydrate oxidation ($P < 0.01$), peaking at 2.60 ± 0.27 kcal/min at a cadence of 45 rev/min. However, fat oxidation was relatively maintained ($P > 0.05$) with increasing exercise intensity.

Reliability data

Over both days of testing, Cronbach's Alpha was calculated for HR, RER, and VO_2 recorded at minute 15 of the protocol, during exercise at 30 rev/min. This coefficient of reliability was equal to 0.79, 0.84, and 0.88 for these variables, suggesting high consistency across multiple bouts of exercise. This data stability allowed us to include the data of subject #1 who only completed 1 day of testing.

Discussion

These data support previous findings (Knechtle et al. 2004) demonstrating that carbohydrate is the primary substrate oxidized during exercise in the SCI. In response to attempted active lower-body and passive upper-body exercise eliciting approximately 50% VO_{2max}, there was a sustained increase in rate of carbohydrate oxidation with

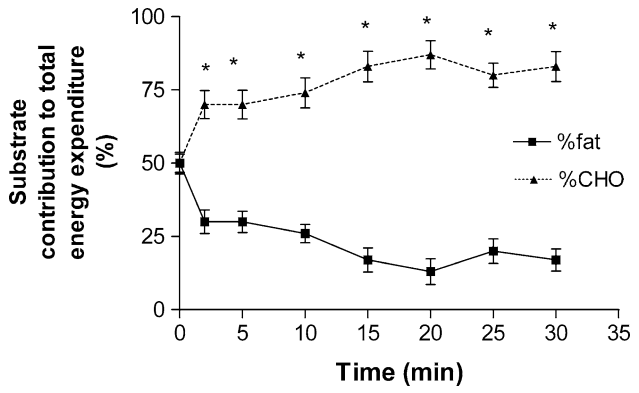

Fig. 1 Percent substrate contribution during combined passive and active exercise in the SCI; cadence was increased from 15, 30 to 45 rev/min every 10 min of exercise after the warm-up. $P < 0.05$ for carbohydrate versus fat

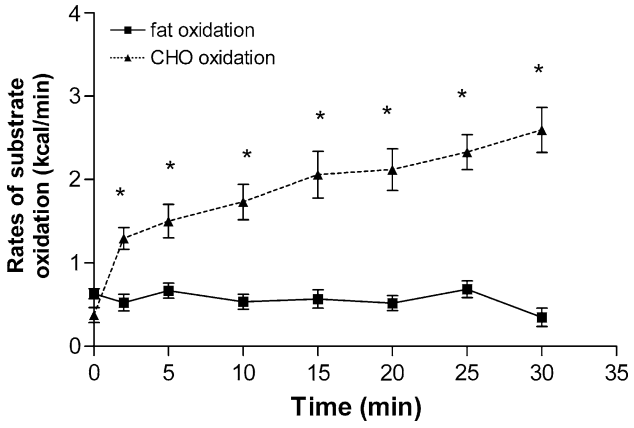

Fig. 2 Rates of substrate oxidation during combined passive and active exercise in the SCI; cadence was increased from 15, 30 to 45 rev/min every 10 min of exercise after the warm-up. $P < 0.05$ for carbohydrate versus fat

increasing VO_2; whereas, fat oxidation was maintained. These findings underscore a substantial reliance on carbohydrate as a substrate during low to moderate intensity exercise in relatively untrained persons with SCI.

To examine substrate utilization during exercise, it is typical to first assess VO_{2max}, and use percentages of VO_{2max} to establish submaximal exercise intensities. However, this was not completed in the present study. Yet, it was assumed that subjects' VO_{2max} ranged from 0.94 to 1.10 L/min, as previously reported (Gass et al. 1981; Wicks et al. 1983) in men with chronic SCI at C5–T4, C7–C8, and C5–T1, similar to injury location of the participants in our study. Using the values for VO_2 recorded during exercise (Table 2), this places the workloads completed at approximately 44–57% VO_{2max}, which could be considered light to moderate exercise. This is similar to workloads used in previous investigations (Knechtle et al. 2003, 2004) examining substrate utilization in the SCI.

The exercise mode used in the present study is similar to that used in previous research examining cardiovascular function in the SCI (Muraki et al. 1996; Figoni et al. 1990). In these studies, VO_2 during passive leg cycle ergometry exercise ranged from 0.25 L/min in paraplegics (Muraki et al. 1996) to 0.29–0.32 L/min in 30 paraplegics and quadriplegics (Figoni et al. 1990), respectively. Passive exercise did not increase VO_2 ($P > 0.05$) compared to rest in either study, yet a 70% increase ($P < 0.05$) was demonstrated in the present study (Table 2). Yet, these authors did not report data pertaining to substrate utilization. In the present study, mean VO_2 at a cadence equal to 45 rev/min was equal to 0.59 ± 0.06 L/min, a lower value than that demonstrated in previous investigations utilizing active leg exercise (Figoni et al. 1990). Seven of nine subjects revealed a dramatic increase in VO_2 (two to three fold) during active exercise (Table 2) when they were asked to resist movement of the machine with their legs, compared to passive warm-up. This suggests that some neural activation in the lower extremities was contributing to the increase in VO_2, although this hypothesis cannot be confirmed without EMG data.

Our data and those from Knechtle et al. (2003) reveal the relative inability of men and women with SCI to rely on fat oxidation during exercise. In that study, arm cranking was completed by elite wheelchair athletes with lower level injuries (T4–L1 and one with injury at C7) at absolute intensities ranging from 1.29 to 1.76 L/min, approximately threefold higher than the peak VO_2 revealed in the present study (Table 2). Rates of fat (2.0–2.1 kcal/min) and carbohydrate (4.5–6.8 kcal/min) oxidation were several fold higher than those in the present study, reflecting a twofold higher energy expenditure of arm cranking versus combined passive and active/attempted exercise completed in the present study. Their subjects were endurance-trained and likely had adaptations including greater mitochondrial mass, lactate threshold, and mitochondrial enzyme activity (Holloszy and Coyle 1984) that allow a relative sparing of carbohydrate during moderate exercise. It is likely that these adaptations were minimal in our subjects, as they were non-athletic. Hence, with initiation of exercise, carbohydrate was the primary source of ATP provision.

One mechanism proposed to explain the reduced reliance on lipid during exercise in the present study is fiber type. It is well-known that in untrained populations, there is typically a greater proportion of type II compared to type I muscle fibers (Essen-Gustavsson and Henriksson 1984). In tetraplegics, composition of the anterior deltoid was 74% type II compared to 57% in paraplegics and 42% in able-bodied (Andersen et al. 1996), and leg muscle was reported to contain more type II muscle in the SCI compared to able-bodied (Schantz et al. 1997). During electrically-stimulated cycling in persons with SCI, there is diminished leg uptake of FFA, increased glucose uptake, and maintenance of insulin release in the SCI (Kjaer et al. 2001). In a study using microdialysis to compare substrate utilization between paraplegics and able-bodied subjects, the exercise-induced increase in lipolysis was lower in paraplegics, which was attributed to lower adipose tissue blood flow, reduced plasma norepinephrine concentration, and higher insulin levels (Stallknecht et al. 2001). Together, these responses would reduce reliance on fat utilization and augment the role of glycolysis to supply ATP during exercise.

One primary limitation of the present study was the small sample of only nine men and women with SCI above T10. Level and completeness of injury varied across subjects, and both tetraplegics and paraplegics were recruited. Yet, fuel oxidation in subjects heterogeneous in these characteristics was also studied in previous research (Knechtle et al. 2003, 2004). A comparison of RER and VO_2 responses for subjects with cervical ($n = 7$) and thoracic ($n = 2$) injuries is revealed in Fig. 3. Resting RER was similar, but tended to be higher during exercise in persons with cervical compared to thoracic injuries, which reflects a greater reliance on carbohydrate. VO_2 was consistently higher during exercise in subjects with thoracic injuries, which may be due to their regular participation (4–6 h/week) in physical activity rather than the location of their injury. Nevertheless, due to the small sample of only two participants with thoracic injuries, these conclusions are preliminary. An additional limitation is the absence of a control group, as was used in other studies (Kjaer et al. 2001; Knechtle et al. 2003) examining fuel utilization in the SCI. The exercise device can only tolerate 60 lb of resistance (Astorino et al. 2008), so able-bodied subjects were not tested. In fact, several subjects damaged the motors; however, this did not impede data collection as

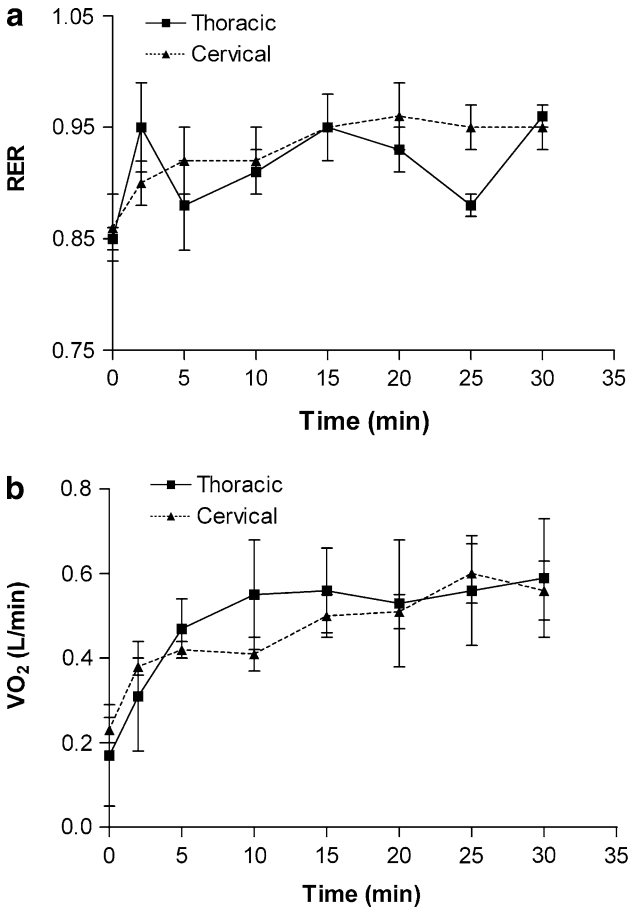

Fig. 3 Comparison of **a** RER and **b** VO_2 responses in subjects with cervical and thoracic injuries

multiple exercise devices were supplied by the manufacturer. Despite these limitations, HR, RER, and VO_2 were consistent across multiple days, which strengthens these findings, albeit in a small sample. Further study is needed to compare substrate utilization in persons with SCI completing exercise at the same absolute intensity who vary in injury level, completeness of injury, and/or fitness status.

The implications of blunted lipolysis in persons with SCI are severe, and include insulin resistance (Duckworth et al. 1980) and increased body fat (Maggioni et al. 2003). Smaller muscle mass has been associated with attenuated muscle glycogen stores (Knechtle et al. 2004), which may impair exercise tolerance. In individuals with SCI, cardiovascular disease risk is higher than in the able-bodied (Bauman and Spungen 2008). Moreover, a positive correlation between serum triglycerides and abdominal circumference has been reported (Bauman et al. 1999). Persons with SCI also have lower serum HDL cholesterol levels than able-bodied individuals (Bauman et al. 1999). Consequently, chronic exercise training should be instituted in individuals with SCI to increase cardiovascular and muscular fitness, which has been shown to improve insulin action, increase reliance on fat, reduce adiposity, and potentially decrease chronic disease risk (Cowell et al. 1986; Dallmeijer et al. 1999).

Conclusion

These findings in non-athletic men and women with SCI reveal that carbohydrate is the preferred substrate during 30 min of mild to moderate exercise. With increasing exercise intensity, there was a relative maintenance in fat oxidation and a gradual increase in reliance upon carbohydrate. This dependence on carbohydrate as a fuel for energy metabolism may be limiting to exercise in this population. Further study is warranted in persons with SCI of similar fitness, yet varying in injury level and completeness of injury, to assess the divergent effect of these characteristics on substrate metabolism.

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